



Attorney Docket No. Q52816  
PATENT APPLICATION

#21  
4/11/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Hiroaki TAKAYAMA, et al.

Appln. No.: 09/214,155

Confirmation No.:

Group Art Unit: 1616

Filed: December 29, 1999

Examiner: Sabiha N. Qazi

For: VITAMIN D3 DERIVATIVE AND ITS PRODUCTION METHOD

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**REQUEST FOR RECONSIDERATION**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

In response to the Office Action dated October 4, 2000, please consider the following remarks.

**I. Non-entry of amendment to specification**

As indicated on page 2 of the Office Action, Applicants' amendment dated August 4, 2000 relating to the specification (inserting the synthetic scheme on page 32) has not been entered on the basis that it is "new matter".

In response, Applicants submit that the correct stereochemistry of the compound (42) is described on page 30 and a person of ordinary skill in the art would easily understand that the resulting product has 2-methyl as the upward configuration.

Further, the title of Example 1 is "Synthesis of (20S) -1  $\alpha$ , 25-dihydroxy-2  $\alpha$ -methyl-3  $\beta$  -vitamin D<sub>3</sub> (72)." Such "2  $\alpha$  -methyl" in this compound means an upward methyl. Thus, it can

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easily be deduced that the stereochemistry of the starting material (42) also has the same configuration.

Accordingly, entry of the amendment is respectfully requested.

**II. Obviousness Rejections**

Claim 3 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Miyamoto et al (U.S. Patent 5,877,168), and claim 4 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Trost M. Barry et al (J. Am. Chem. Soc., Vol. 114, No. 25, (1992), pages 9836-45.

**A. The Examiner's Position**

In the Office Action at page 3, the Examiner recognizes that the Declaration shows better results for the instant invention with 20(S), but questions why the concentration of each tested compound varies. The Examiner specifically requests Applicants to explain why the concentration used is different in various tested compounds.

**B. Applicants' Response**

In response, Applicants submit that the different range of concentration depending on the individual compound is an ordinary matter, because usually scientists would find out a suitable concentration range in order to clearly show the biological activity of the tested compound. Since the figure in this experiment could range from zero to 100%, a researcher will have meaningless data if the proper concentration for the individual compound is not selected. In

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other words, data around 0 or data around 100 are not useful for comparison, because one cannot conclude which compound has higher biological activity where both compounds have about 100% activity or about 0% activity. Dr. Ishizuka selected and showed a proper range for comparison depending on biological activity of individual compound. In any event, Applicants submit that it is reasonable to conclude that **a compound having the same or higher biological activity at lower concentration has higher biological activity**. Comparison at the same concentration is not always required.

Further, Applicants provide below additional data adopting higher concentrations of compounds (68), (71), (72) and (74).

Compounds	NBT Positive Cells %(Mean±SD; n=3)					
	10 <sup>-7</sup> M	10 <sup>-8</sup> M	10 <sup>-9</sup> M	10 <sup>-10</sup> M	10 <sup>-11</sup> M	10 <sup>-12</sup> M
(65)	95.1 ±2.8	32.0±3.2	1.4±0.8	1.8±0.7		
(68)			95.7±1.0	57.7±5.0	2.8±0.7	1.7±0.3
(3)	1.4±0.2	1.8±0.7	1.3±0.5	1.6±1.1		
(71)			40.5±1.8	2.0±1.0	1.8±0.8	1.5±0.8
(4)	95.9±1.1	93.9±4.4	69.4±3.9	2.3±0.9		
(72)			96.2±2.0	95.7±2.3	94.4±1.8	3.7±0.8
(6)	92.7±2.9	12.9±2.2	1.8±0.2	1.9±0.6		
(74)			96.4±1.4	16.7±1.1	17.0±2.3	6.4±1.1

Compounds	NBT Positive Cells %(Single assay)			
	10 <sup>-7</sup> M	10 <sup>-8</sup> M	10 <sup>-9</sup> M	10 <sup>-10</sup> M
(68)	99.5	98.0	98.3	90.8
(71)	97.7	97.5	47.1	22.0
(72)	98.6	98.6	97.9	93.7
(74)	98.7	97.7	95.4	52.1

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The upper table data is substantially the same as that provided previously by Dr. Ishizuka, with some difference in detail. If the Examiner wishes, Applicants can submit a Declaration under 37 C.F.R. §1.132 in regard to the additional data.

In view of the above, Applicants respectfully submit that the present invention is not obvious. Accordingly, withdrawal of these rejections is respectfully requested.

**III. Obviousness-type Double Patenting Provisional Rejection**

The Office Action states that the claims are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, based on claims 3 and 4 of copending Application No. 09/068,219.

**A. The Examiner's Position**

The Examiner views the instant claims (to the 20S compounds) as obvious over the claims in co-pending Application No. 09/068,219 (to the 20R compounds).

The Examiner states that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**B. Applicants' Response**

The Examiner indicated "In the instant applications applicants are claiming 20-S compounds whereas in 09/068,219 the compound with 20-R are claimed." This is correct. However, Applicants submit that the phrase "these compounds are considered obvious over the

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other" cannot be applied to the compounds at issue, because 20-S compounds are higher biological effect compared to 20-R compounds as shown in Dr. Ishizuka's Declaration.

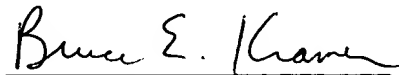
That is, the order of biological effect is: prior art compounds << 20-R compounds << 20-S compounds. Therefore, Applicants submit that the 20-S compounds and 20-R compounds are patentably distinct.

Thus, reconsideration and withdrawal of the obviousness-type double patenting rejection is respectfully requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicants hereby petition for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



Bruce E. Kramer  
Registration No. 33,725

SUGHRUE, MION, ZINN,  
MACPEAK & SEAS, PLLC  
2100 Pennsylvania Avenue, N.W.  
Washington, D.C. 20037-3213  
Telephone: (202) 293-7060  
Facsimile: (202) 293-7860  
Date: April 4, 2001